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ORIGINAL ARTICLE

Association between hematologic parameters and in-hospital mortality in patients with infective endocarditis

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Abstract Early and accurate risk prediction is an important clinical demand in patients with infective endocarditis (IE). The platelet-to-lymphocyte ratio (PLR) is an independent predictor of worse prognosis in various cardiovascular diseases. The aim of this study was to determine the value of PLR in the prediction of in-hospital mortality among IE patients. We retrospectively analyzed the clinical, laboratory, and echocardiographic data of 59 adult patients with definite IE and in 40 adult controls. In-hospital mortality occurred in 16 (27%) patients. Vegetation size, levels of high-sensitive C-reactive protein and procalcitonin, neutrophil-to-lymphocyte ratio, and PLR were significantly higher in the in-hospital-mortality-positive group than in the in-hospital-mortality-negative group ($p = 0.004$, $p = 0.009$, $p = 0.030$, $p = 0.001$, and $p = 0.008$, respectively). Lymphocyte count was, however, significantly lower in the in-hospital-mortality-positive group ($p = 0.004$). In the receiver-operating characteristic analysis, PLRs over 191.01 predicted in-hospital mortality with 56.3% sensitivity and 81.4% specificity [area under the curve 0.725, 95% confidence interval (CI) 0.594–0.833; $p = 0.0027$]. In the multivariate analysis, PLR was found to be an independent predictor of in-hospital mortality in patients with IE (odds ratio 1.022, 95% CI 1.003–1.042; $p = 0.021$). In conclusion, higher PLR may predict in-hospital mortality in patients with IE.

Conflicts of interest: All authors declare no conflicts of interest.

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Introduction

Infective endocarditis (IE) is the infection of heart valves, large intrathoracic vessels, and intracardiac foreign bodies such as the interventricular septum, chordae tendineae, or mural endocardium. Despite the improvements in the diagnosis and treatment of IE, the in-hospital mortality and morbidity rates of this infection remain high [1—4]. Echocardiographic findings, clinical characteristics, and blood parameters, such as high-sensitive C-reactive protein (hsCRP) level and white blood cell (WBC) counts, are well-established markers for disease monitoring [1,5—7]. In recent years, with the growing understanding of the role of various inflammatory markers in IE, studies have focused on new, widely available, and inexpensive inflammatory markers. In this regard, recent studies have revealed that various markers including WBC count, neutrophil-to-lymphocyte ratio (NLR), and mean platelet volume are associated with IE and its prognosis [4,8—10].

Platelets are well-established components of the hemostatic system. Recently, several additional functions of platelets have been demonstrated in the pathogenesis of various diseases in which inflammation is an important clinical sign. Besides, lymphocyte count is inversely correlated with inflammation, and thus, a lower lymphocyte count indicates an increased risk of cardiovascular disease and mortality [11,12]. The platelet-to-lymphocyte ratio (PLR) is positively correlated with inflammation, and therefore, can be a useful biomarker to predict inflammation. The PLR is an easily applicable blood test, and can be performed using a complete blood count analyzer. Moreover, the test does not require any complex or expensive technologies [13,14]. Recently, PLR was used as a worse prognostic marker of various cardiovascular conditions [15—18]. However, there are no data regarding its predictive role in patients with IE. In this study, we aimed to assess the relationship between PLR levels obtained on admission and in-hospital mortality in patients with IE.

Methods

We retrospectively analyzed clinical, laboratory, and echocardiographic data of 62 consecutive adult patients with definite IE diagnosis between January 2012 and February 2015 at Adnan Menderes University School of Medicine, Aydin, Turkey and Celal Bayar University School of Medicine, Manisa, Turkey. Both centers were using standardized protocols, uniform data collection methods, and identical diagnostic and therapeutic criteria for IE. The study protocol was approved by the Adnan Menderes University School of Medicine Ethics Committee and the Institutional Review Board. All patients met the modified Duke criteria for the definitive diagnosis of IE [5]. Diagnostic categories were defined as follows: direct evidence of vegetative growth in a histologic or bacteriologic study of the involved tissue or satisfying two major criteria or one major and three minor criteria or five minor criteria for IE. Three patients were excluded from the study because of missing data, and thus data on 59 patients were analyzed in this study. The healthy volunteers group included individuals who were admitted to the cardiology outpatient unit for check-up. After these exclusions, the final study population consisted of 59 patients with IE and age-, sex-matched 40 healthy volunteers (control group).

All clinically relevant data of the patients were stored in an electronic database. Data collected included patients' characteristics; laboratory measurements; echocardiographical, microbiological, and pathological findings; need for surgical valve replacement of the infected valve; and clinical course of the disease. Microbial pathogens were detected according to standard methods and established microbiological guidelines. All patients were followed up until their discharge from hospital.

Venous blood samples of all patients were collected at hospital admission, and at least three separate venipuncture sites were used for collecting blood samples (for sample culture) with 1-hour intervals. Additional samples were also drawn to examine various specific antibodies. The extracted tissues during surgery were sent for culture. The biochemical analysis including glucose, urea, creatinine, total protein, albumin, globulin were measured Architect C8000 analyzer (Abbot Park, IL, USA). hsCRP were also measured in the collected blood samples. Procalcitonin levels were measured by the chemiluminescent immunoassay using an auto-analyzer (Maglumi 600, Shaanxi, China) and hsCRP levels were analyzed using a Beckman Coulter AU Analyzer (Beckman Coulter, IMMAGE, Immunochemistry System, USA) in all blood samples. Complete blood count (CBC) parameters were measured using a Sysmex K-1000 auto-analyzer (Block Scientific, Bohemia, NY, USA). PLR was directly calculated from CBC results.

Echocardiography (Vivid S5, GE Vingmed Ultrasound A/S, Horten, Norway) with a 3.5-MHz transducer was performed and the following data were recorded: left ventricular ejection fraction (LVEF), presence and length of vegetation, and presence and degree of valvular dysfunction. The presence of a myocardial abscess was considered based on echocardiographical and surgical findings. LVEF was calculated according to the Simpson method and patients with LVEF above 55% were considered to have normal systolic function.

All statistical analyses were carried out using SPSS version 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Continuous variables were tested for normal distribution by the Kolmogorov—Smirnov test. Data on continuous variables were reported as mean and standard deviation or median (min—max). Continuous variables were compared using the Student *t* test or Mann—Whitney *U* test between groups. Categorical variables were summarized as percentages and compared with the Chi-square test. Receiver-operating characteristic (ROC) curve analysis was used to determine optimal cutoff values of PLR levels to predict the in-hospital mortality rate in patients with IE. To determine the independent predictors of in-hospital death, clinical parameters were evaluated by stepwise forward logistic regression analysis. Multivariate logistic regression analysis was used to identify independent predictors of in-hospital mortality in patients with IE. The survival curve of PLR during hospitalization was analyzed using the Kaplan—Meier method, and statistical assessment was performed using the log-rank test. A two-tailed p value < 0.05 was considered statistically significant for all analyses.

Results

There were 59 patients (mean age 58.5 ± 14.7 years and 25 men) in the IE group and 40 volunteers (mean age 56.9 ± 10.0 years and 22 men) in the control group. Baseline characteristics and laboratory parameters are shown in Table 1. Patients in the IE group had significantly lower LVEF (52.4 ± 11.1% vs. 63.5 ± 4.6%, $p < 0.001$) than those in the control group.

With respect to laboratory analyses, creatinine [1.00 mg/dL (0.56–8.06 mg/dL) vs. 0.78 mg/dL (0.64–1.17 mg/dL), $p = 0.001$] and urea levels [45.0 mg/dL (13.0–184.0 mg/dL) vs. 33.0 mg/dL (17.0–79.0 mg/dL), $p = 0.001$] were significantly higher in the IE group than in the control group, whereas the albumin (3.19 ± 0.62 g/dL vs. 4.00 ± 0.47 g/dL, $p < 0.001$) levels were significantly lower in the IE group. Erythrocyte sedimentation rate [81 hours (25–121 hours) vs. 22 hours (7–38 hours), $p < 0.001$], hsCRP [118.0 mg/L (18.8–280.0 mg/L) vs. 1.9 mg/L (0.3–7.8 mg/L), $p < 0.001$], and procalcitonin [1.96 ng/mL (0.08–100.00 ng/mL) vs. 0.12 ng/mL (0.01–0.41 ng/mL), $p < 0.001$] levels were also significantly higher in the IE group than in the control group.

The CBC test results are as follows: neutrophil count (11.8 ± 5.9 × 10^3 μL vs. 4.6 ± 1.4 × 10^3 μL, $p < 0.001$) and PLR [133.6 (27.2–677.8) vs. 109.9 (50.6–225.4), $p = 0.026$] levels were significantly higher in the IE group. However, lymphocyte count (1.7 ± 0.7 × 10^3 μL vs. 2.4 ± 0.7 × 10^3 μL, $p < 0.001$) was significantly lower in the IE group. Platelet count (220.6 ± 99.2 × 10^3 μL vs. 252.7 ± 53.0 × 10^3 μL, $p = 0.064$) was similar between the two groups. The NLR was significantly higher in the IE group than in the control group [7.1 (1.2–38.9) vs. 2.1 (0.9–3.4), $p < 0.001$].

Patients with IE were divided into two groups (mortality-positive and mortality-negative groups) according to in-hospital mortality (Table 2). Vegetation size, hsCRP, procalcitonin, NLR, and PLR were significantly higher in the in-hospital-mortality-positive group than in the mortality-negative group ($p = 0.004$, $p = 0.009$, $p = 0.030$, $p = 0.001$, and $p = 0.008$, respectively). Lymphocyte count was, however, significantly lower in the in-hospital-mortality-positive group ($p = 0.004$).

The ROC curve of PLR for predicting in-hospital mortality is shown in Figure 1. A PLR level over 191.01, measured upon admission, had 56.3% sensitivity and 81.4% specificity in its association with in-hospital mortality [area under the curve 0.725, 95% confidence interval (CI) 0.594–0.833; $p = 0.0027$]. Figure 2 presents the Kaplan–Meier curve for in-hospital mortality according to the cutoff value of PLR in patients with IE (log-rank; $p = 0.019$).

Some variables associated with in-hospital mortality in patients with IE were significantly different between the mortality-positive and mortality-negative groups. The independent contributions of age, sex, erythrocyte sedimentation rate, hsCRP, procalcitonin, hemoglobin, WBC, lymphocyte, PLR, NLR, urea, creatinine, albumin, *Staphylococcus aureus*, vegetation size, and LVEF were analyzed

Table 1 Baseline characteristics.

Variables	Infective endocarditis ($n = 59$)	Healthy controls ($n = 40$)	p
Age (y)	58.5 ± 14.7	56.9 ± 10.0	0.552
Sex (female/male)	34/25	18/22	0.479
Diabetes mellitus	18 (31)	11 (28)	0.464
Hypertension	19 (32)	18 (45)	0.140
Smoker	13 (22)	10 (25)	0.457
Laboratory results			
Glucose (mg/dL)	130.3 ± 64.9	109.7 ± 40.4	0.076
Urea (mg/dL)	45.0 (13.0–184.0)	33.0 (17.0–79.0)	0.001
Creatinine (mg/dL)	1.00 (0.56–8.06)	0.78 (0.64–1.17)	0.001
Total protein (g/dL)	6.58 ± 0.84	6.96 ± 0.54	0.090
Albumin (g/dL)	3.19 ± 0.62	4.00 ± 0.47	<0.001
Globulin (g/dL)	3.36 ± 0.73	3.10 ± 0.48	0.062
Erythrocyte sedimentation rate (h)	81 (25–121)	22 (7–38)	<0.001
hsCRP (mg/L)	118.0 (18.8–280.0)	1.9 (0.3–7.8)	<0.001
Procalcitonin (ng/mL)	1.96 (0.08–100.00)	0.12 (0.01–0.41)	<0.001
Hemogram			
Hemoglobin (g/dL)	10.3 ± 1.7	13.3 ± 1.7	<0.001
Platelet (×10^3 μL)	220.6 ± 99.2	252.7 ± 53.0	0.064
White blood cell (×10^3 μL)	14.5 ± 6.3	7.9 ± 1.9	<0.001
Neutrophil (×10^3 μL)	11.8 ± 5.9	4.6 ± 1.4	<0.001
Lymphocyte (×10^3 μL)	1.7 ± 0.7	2.4 ± 0.7	<0.001
Neutrophil-to-lymphocyte ratio	7.1 (1.2–38.9)	2.1 (0.9–3.4)	<0.001
Platelet-to-lymphocyte ratio	133.6 (27.2–677.8)	109.9 (50.6–225.4)	0.026
Echocardiography result			
LVEF (%)	52.4 ± 11.1	63.5 ± 4.6	<0.001

Data are presented as n (%), mean ± standard deviation, or median (min–max).
hsCRP = high-sensitive C-reactive protein; LVEF = left ventricular ejection fraction.

Table 2 Baseline characteristics between in-hospital-mortality-positive and in-hospital-mortality-negative groups.

Variables	In-hospital mortality		*p*
	Positive group (n = 16)	Negative group (n = 43)	
Men age (y)	61.2 ± 9.8	57.5 ± 16.2	0.396
Sex (Female/Male)	8/8	26/17	0.333
Diabetes mellitus	3 (18.8)	15 (34.9)	0.192
Chronic renal failure	4 (15)	9 (20.9)	0.495
Hospitalization time (d)	42.6 ± 36.1	47.3 ± 36.1	0.654
Previous infective endocarditis	1 (6.3)	2 (4.7)	0.620
LVEF (%)	47.9 ± 11.4	54.1 ± 10.6	0.056
Vegetation size (mm)	16.1 (11.0–35.2)	10.2 (3.1–37.4)	0.004
Surgical therapy	2 (12.5)	14 (32.55)	0.110
Infective endocarditis localization			
Native valve	8 (50)	27 (62.)	0.276
Prosthetic valve	8 (50)	11 (25.6)	0.072
Pacemakers	0 (0)	5 (11.6)	0.192
Staphylococcus aureus	9 (56.3)	14 (32.6)	0.097
Erythrocyte sedimentation rate (h)	68.4 ± 30.9	78.8 ± 25.3	0.203
hsCRP (mg/L)	157.7 (73.9–280.7)	103.0 (18.8–273.4)	0.009
Procalcitonin (ng/mL)	6.29 (0.18–70.27)	1.24 (0.08–100.00)	0.030
Hemoglobin (g/dL)	10.2 ± 1.8	10.3 ± 1.7	0.775
Platelet ($\times 10^3$ μL)	224.0 ± 93.5	219.4 ± 102.2	0.874
White blood cell ($\times 10^3$ μL)	15.5 ± 7.1	14.1 ± 6.0	0.442
Neutrophil ($\times 10^3$ μL)	13.1 ± 6.8	11.4 ± 5.5	0.332
Lymphocyte ($\times 10^3$ μL)	1.23 ± 0.51	1.85 ± 0.75	0.004
Neutrophil-to-lymphocyte ratio	11.9 ± 7.6	6.7 ± 3.6	0.001
Platelet-to-lymphocyte ratio	199.0 (81.2–677.8)	123.2 (27.2–364.0)	0.008

Data are presented as n (%), mean ± standard deviation, or median (min–max).
hsCRP = high-sensitive C-reactive protein; LVEF = left ventricular ejection fraction.

using multivariate logistic regression (Table 3). In the multivariate model, the PLR [odds ratio (OR) 1.022, 95% CI 1.003–1.042; p = 0.021], NLR (OR 1.337, 95% CI 1.037–1.724; p = 0.025), lymphocyte (OR 0.011, 95% CI 0.001–0.377; p = 0.013), vegetation size (OR 1.169, 95% CI 1.014–1.348; p = 0.032), and hsCRP (OR 1.029, 95% CI 1.002–1.058; p = 0.036) remained independent predictors of in-hospital mortality (Table 3).

Discussion

In this study, we investigated the predictive role of different variables in in-hospital mortality of patients with definite IE diagnosis. The main findings of this study were as follows: the PLR is significantly higher in patients with IE than in healthy controls and higher PLR level on admission is an independent predictor of in-hospital mortality in patients with IE.

IE is a life-threatening heart disease, which involves complex inflammatory processes. Various factors may contribute to the pathogenesis of IE such as underlying predisposing heart condition, immune deficiency and related comorbid conditions, addiction of intravenous drugs, and some causative microorganisms [1]. The in-hospital mortality rates for IE continue to remain high (ranging from 15% to 40%) despite significant improvements in medical technologies [6]. Despite developments in the field of medicine, the management, diagnosis, and prediction of IE are challenging.

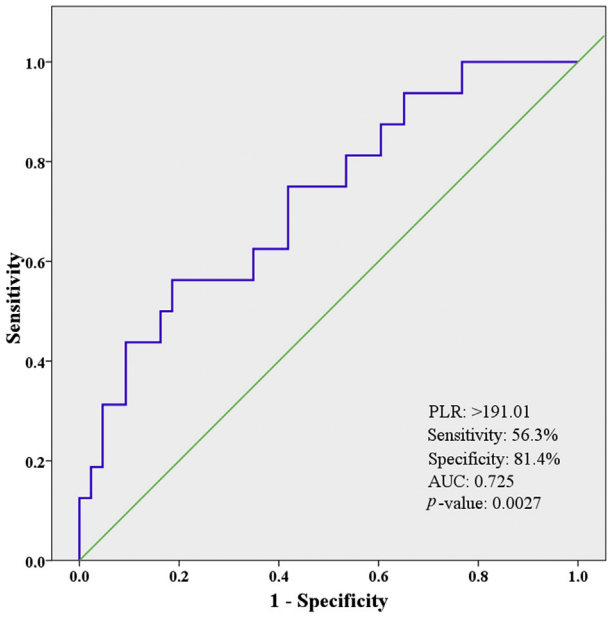

Figure 1. The receiver-operating characteristic curve of platelet-to-lymphocyte ratio (PLR) for predicting angiographic in-hospital mortality in patients with infective endocarditis. AUC = area under the curve.

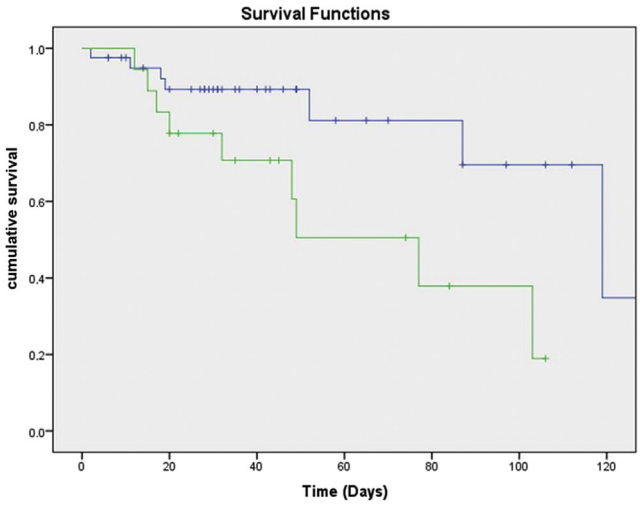

Figure 2. Kaplan—Meier curve for in-hospital mortality according to the cutoff value of platelet-to-lymphocyte ratio in patients with infective endocarditis (log rank, $p = 0.019$).

Echocardiographic findings, clinical characteristics, and blood count parameters are well-established markers for the diagnosis and monitoring of this infection [1,5,6]. Conventional and easily available markers such as the hsCRP level and total WBC counts have been widely used for assessment of IE [7]. Accordingly, higher total WBC count on admission has been shown to be a significant and independent predictor of mortality in patients with IE [8].

Regardless of the fact that a number of biomarkers have been found to be related with the prognosis of IE, they are still not routinely used in clinical practice, except echocardiographic findings (such as vegetation size) and hsCRP. Thus, it is worthwhile and necessary to investigate new, widely available, and inexpensive predictors for IE. In recent years, with the growing understanding of the role of various inflammatory markers in IE, studies have been focused on other inflammatory markers. Turak et al. [9] retrospectively analyzed 121 patients with definite IE and hypothesized that increased NLR level on admission would predict unfavorable in-hospital outcomes. They showed that NLR on admission is an independent predictor of in-hospital mortality in IE cases [9]. Bozbay et al. [10] also investigated the role of NLR in IE. They found an independent association between NLR and in-hospital mortality in patients with IE. However, there was not any association between NLR and long-term outcomes. In our study, consistent with the literature, hsCRP and NLR were significantly higher in patients with IE than in healthy controls. In addition, vegetation size, hsCRP, and NLR were independently associated with in-hospital mortality in patients with IE. However, to the best of our knowledge, there is no similar study assessing the association of PLR with IE and in-hospital mortality.

In recent years, an association between PLR and various cardiovascular disorders has been demonstrated. It has been clearly demonstrated that higher PLR on admission is independently associated with worse clinical outcomes in patients with coronary artery disease during both in-hospital stays and long-term follow-up periods [19—21]. CBC is a widely available and inexpensive test that provides important data about the properties of various blood cells such as platelets and lymphocytes. Platelets are well-established components of the hemostatic system. Recently, several additional functions of platelets have been demonstrated, especially in the process of inflammation. There is growing data about the critical role of platelets in inflammation. Platelets release numerous inflammatory mediators. Many of these mediators modify leukocyte and endothelial responses via different inflammatory stimuli [22]. Owing to their interactions with neutrophils, lymphocytes, and the endothelium, platelets play a pivotal role in inflammation

Table 3 Effects of multiple variables on the in-hospital mortality in univariate and multivariate regression analysis.

Variables	Unadjusted OR	*p*	Adjusted OR[a]	*p*
Age	1.006 (0.967—1.047)	0.755		
Sex	1.231 (0.445—3.406)	0.690		
Erythrocyte sedimentation rate	0.988 (0.970—1.006)	0.201		
hsCRP	1.008 (1.000—1.016)	0.058	1.029 (1.002—1.058)	0.036
Procalcitonin	1.011 (0.992—1.030)	0.269		
Hemoglobin	1.035 (0.789—1.358)	0.804		
White blood cell	1.036 (0.947—1.133)	0.437	1.012 (0.898—1.140)	0.845
Lymphocyte	0.205 (0.064—0.659)	0.008	0.011 (0.001—0.377)	0.013
Platelet-to-lymphocyte ratio	1.003 (1.000—1.006)	0.030	1.022 (1.003—1.042)	0.021
Neutrophil-to-lymphocyte ratio	1.333 (1.073—1.657)	0.010	1.337 (1.037—1.724)	0.025
Urea	1.011 (0.999—1.022)	0.079	0.988 (0.956—1.021)	0.472
Creatinine	0.975 (0.730—1.303)	0.866		
Albumin	0.429 (0.164—1.120)	0.084	0.327 (0.043—2.489)	0.280
Staphylococcus aureus	1.931 (0.714—5.219)	0.195		
Vegetation size	1.072 (1.008—1.140)	0.028	1.169 (1.014—1.348)	0.032
LVEF %	0.976 (0.938—1.016)	0.234		

hsCRP = high-sensitive C-reactive protein; LVEF = left ventricular ejection fraction; OR = odds ratio.
[a] Adjusted for hsCRP, white blood cell, lymphocyte, platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, urea, albumin, vegetation size.

and both innate and adaptive immune responses. Numerous research groups have shown the important roles of platelets in the pathogenesis of various inflammatory clinical conditions. In previous epidemiological studies, platelet counts were found to be elevated in patients with chronic inflammatory diseases, malignancies, and myeloproliferative disorders [23,24]. Moreover, epidemiological evidence also supports the fact that antiplatelet medications may affect host immunity. Besides, they were also associated with reduced mortality in patients with sepsis, without causing excessive bleeding in these patients [25,26].

Lymphocytopenia is a common finding in chronic inflammatory conditions because of increased stress and consequent lymphocyte apoptosis. Mechanisms of lymphocytopenia are apoptosis due to proinflammatory cytokines, increased catecholamine and cortisol levels, and redistribution of lymphocytes to lymphatic organs [27,28]. Previous studies have demonstrated that lymphocytopenia is independently associated with the severity of infectious disease and bacteremia [29,30].

Because PLR is a ratio, it is relatively more stable than individual blood parameters, which may be altered by several variables (e.g., dehydration, overhydration, and blood specimen handling) [31]. The advantage of PLR calculation could be that it reflects the condition of both aggregation and inflammatory pathways and it may be more valuable than either platelet or lymphocyte count alone in the prediction of various inflammatory diseases including cardiovascular diseases [19,32]. In a previous study, Azab et al. [33] showed that lower lymphocyte and higher platelet counts were significantly related to worse prognosis in patients with non-ST-elevation myocardial infarction. They also showed that the effect of PLR on mortality was independent of platelet or lymphocyte counts alone. Besides, in another study, Gary et al. [34] reported that PLR was significantly correlated with inflammatory indicators such as C-reactive protein and fibrinogen in patients with limb ischemia. In the light of previous studies on PLR, it can be rationale to hypothesize that there may be associations between PLR, IE, and in-hospital mortality.

The limitations of our study were its retrospective design and the presentation of only two-center experiences. The study has a relatively small sample size, and these results should be confirmed by further studies. In this study, we especially focused on the assessment of the relation between PLR levels on admission and in-hospital mortality. We designed the study protocol in this direction and performed our analyses solely based on blood test results at admission.

Our study is the first clinical study demonstrating that PLR levels are significantly higher in IE patients and independently associated with in-hospital mortality of these patients. The PLR, which can be easily measured from CBC data, is a simple, widely available, and inexpensive parameter. Thus, PLR may be a useful marker for monitoring IE and predictor of in-hospital mortality in patients with IE.

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